The Treatment of Infectious Diseases

Advances in the Use of Antimicrobial Drugs

H. CORWIN HINSHAW, M.D., San Francisco

• Penicillin remains the most useful antibiotic for treatment of infections due to organisms sensitive to this drug because of its bacteriocidal properties and its freedom from toxicity. Enormous doses may broaden its antibacterial spectrum and it may act synergistically with certain other drugs.

New penicillin compounds have been developed which serve such special purposes as (1) concentration in lung tissue, (2) maintenance of therapeutic concentrations in the blood for long periods after injection, (3) avoidance of allergic reactions and (4) prolongation of therapeutic content in the blood after oral administration.

Erythromycin and carbomycin may be effective against bacterial infections not sensitive to other antibacterial drugs.

Streptomycin combined with dihydrostreptomycin is less toxic than is either drug used alone.

Isoniazid is a valuable antituberculosis drug, especially when combined with streptomycin.

Viomycin may be useful in treating tuberculous infections that have become resistant to other specific drugs.

THIS PRESENTATION is intended to evaluate briefly some recent significant advances in specific antibacterial therapy with penicillin, erythromycin, carbomycin, streptomycin, viomycin and isoniazid.

The commanding position of penicillin among antibiotics has been maintained and even advanced by recent developments. It has at least four outstanding valuable attributes: (1) It is bacteriocidal in high concentrations. (2) High concentrations in blood and tissue are attainable, since dosage may be increased almost without limit, if necessary, without toxic effect. (3) High concentrations also broaden the spectrum of activity of this drug. (4) Penicillin acts synergistically with some other drugs.

Bacteriocidal action may be necessary for the cure of some chronic infections, such as subacute bacterial endocarditis, although bacteriostasis is adequate for the cure of some acute diseases with natural immunity mechanisms, such as pneumonia. Massive doses of penicillin, from 10 million to 100 million units daily, given intravenously, may have bacteriocidal effects not possible with conventional doses. When it is given in such quantities the sodium salt of penicillin G should be used rather than the potassium salt to avoid serious potassium intoxication.

Although it has been referred to as a narrow spectrum antibiotic, penicillin may better be designated a highly specific antibiotic, for it may be much more potent than any other substance against certain infections. When given in massive doses it is effective against many kinds of pathogenic agents that are not affected by usual doses. A bacteriologist is often an indispensable consultant to a clinician dealing with serious bacterial infections, for the best choice of drug or combination of drugs and the dose necessary may depend upon sensitivity tests in vitro.

The action of penicillin is sometimes considerably enhanced by use of another antibacterial drug with it. Bacitracin or streptomycin combined with penicillin may kill bacteria which are relatively insensitive to either of these antibiotics alone. It is also true that combinations may be less effective than penicillin alone, especially when the second drug is one of the so-called broad spectrum antibiotics, such as aureomycin, chloramphenicol, or terramycin.

The clinical usefulness of penicillin has been enhanced with the appearance of new special purpose penicillin compounds. Four types of such compounds that have been developed recently deserve special mention:

1. Penethamate hydriodide (penicillin G diethylaminoethyl ester hydriodide) concentrates in lung tissue and in pulmonary secretions more than in other organs. Chronic pulmonary infections, including bronchiectasis and pulmonary abscess, may respond to treatment with this ester of penicillin in moderate doses. Large doses of procaine penicillin may yield similar results. As iodine content of penethamate hydriodide is considerable, the drug may be useful as an expectorant, but it cannot be given

Presented before the Section on General Medicine at the 82nd Annual Session of the California Medical Association, Los Angeles, May 24-28, 1953.

to patients who have idiosyncratic sensitivity to iodides.

2. Dibenzyl-ethylene-diamine dipenicillin (DBED dipenicillin) is most remarkable for the fact that a single injection (600,000 to 1,200,000 units) may maintain the content of the drug in the blood at a low therapeutic level for from two to four weeks. Its greatest field of usefulness is thought to be in the prophylaxis of rheumatic fever but it opens a possible field for study of specific prevention of some other infectious diseases as well.

3. Allergic sensitivity to penicillin is frequently troublesome and substantial progress toward prevention of such reactions has been made since the appearance of hypoallergic penicillin compounds, especially 1-ephenamine penicillin and penicillin "O." These compounds may be tolerated by patients with a history of cutaneous allergic reaction to penicillin.

4. Oral penicillin therapy is more feasible now that sustained content in the blood may be realized for at least eight hours after a single dose of 200,000 units of either dibenzyl-ethylene-diamine dipenicillin or a combination of penicillin G with probenecid.

Erythromycin and carbomycin are new antibiotics with a spectrum of activity similar to that of penicillin. It is by no means clear when they should be chosen in preference to the better known antibacterial drugs unless in vitro tests indicate that the organism in question is more sensitive to one of the new preparations. Many penicillin-resistant staphylococci and non-hemolytic streptococci are found to be sensitive to erythromycin and to carbomycin. There is some cross resistance between erythromycin and carbomycin but the two drugs are not identical. They do not have the same range of bacteriocidal possibilities that penicillin has, and unlike penicillin they cannot be given in massive doses.

The neurotoxic potentialities of streptomycin have now been reduced substantially by the practice of combining streptomycin with dihydrostreptomycin. The logic of this combination is very simple: Since streptomycin toxicity is ordinarily limited to an effect upon functions of the vestibular branch of the eighth cranial nerve, and the toxicity of dihydrostreptomycin, which has similar therapeutic effect, ordinarily affects only the auditory branch of this nerve, combining them in equal amounts greatly reduces the risk of toxic damage without sacrifice of therapeutic value. Animal experiments and clinical studies have shown that this advantage is realized.

Streptomycin neurotoxicity is rarely observed, regardless of the type of streptomycin used, if dosage is limited to 1 gm. given every second or third day; and this amount is adequate to control most chronic tuberculous infections when combined with para-aminosalicylic acid (12.0 gm. daily). These drugs are usually given for a period of one year or more in the treatment of chronic pulmonary tuberculosis.

Nearly all patients with active tuberculosis now receive specific antibacterial drug therapy and often conservative collapse therapy. Pulmonary resection of residual foci of inactive disease remaining after nine to twelve months of specific medical treatment is frequently recommended as a means of preventing subsequent relapse. Such treatment more nearly approaches curative and definitive therapy than any used heretofore.

Isoniazid has now been studied clinically for more than a year in many institutions and its usefulness and limitations are becoming well established. When used alone it is often inadequate to control chronic tuberculosis because of the early appearance of resistant bacilli, frequently within two or three months. When it is combined with streptomycin there is striking added therapeutic benefit and some delay in the appearance of resistant bacilli. Isoniazid is an extremely valuable preventive of tuberculous complications of pulmonary resection, and some surgeons have urged that if intrathoracic operation is contemplated, isoniazid not be used until the time of operation. Isoniazid diffuses through tissues more readily than do other antituberculosis drugs and appears in the cerebrospinal fluid freely. For this reason it has become a very valuable addition to streptomycin and para-aminosalicylic acid in the treatment of tuberculous meningitis.

Viomycin, a new antibiotic useful for the treatment of tuberculosis, is now available commercially. Its precise place in relation to other antituberculosis drugs is not clear, except that it is of value in the treatment of infections that have become resistant to the more familiar drugs. With the appearance of new specific drugs such as isoniazid and viomycin, the plight of patients with an infection resistant to streptomycin and para-aminosalicylic acid is not so serious as it formerly was. The need for precise bacteriologic studies of drug resistance has become obvious and has been met in most hospitals and sanatoriums.

490 Post Street.